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EXAMINER

MCGARRY, SEAN

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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Application Number: 09/964,667
Filing Date: September 28, 2001
Appellant(s): DE LA MONTE ET AL.

Frank Cottingham
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/01/05 appealing from the Office action
mailed 6/01/04.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appellant has listed related Appeals at page 4 of the Brief filed 4/08/05.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection is substantially correct. The changes are as follows: Applicant appears to have separated the grounds of rejection of the invention based on antisense oligonucleotides and ribozymes. The claimed methods

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using either of the nucleic acid based antisense oligonucleotides and ribozymes are rejected for the same reasons and are not treated separately in the rejection of record.

Note that the claims drawn to method using antisense oligonucleotides and ribozymes were rejoined in the Official Action mailed 9/9/04. Both "Grounds" of rejection will be treated together as they have been in the rejection of record.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

The following is a listing of the evidence (e.g., patents, publications, Official Notice, and admitted prior art) relied upon in the rejection of claims under appeal.

Agrawal, S., TIBTECH, Vol. 14:376-387, October 1996.

Branch, A., TIBS Vol. 23, February 1998.

Jen et al., STEM CELLS Vol. 18:307-319, 2000.

Galderisi et al., J. Cell. Physiol. Vol. 181:251-257, 1999.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 37-42, 43, and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed invention is drawn to the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas via the administration of antisense based nucleic acid based compounds. The compounds are antisense and ribozymes which correspond to a sequence of NTP mRNA defined by nucleotides 150-1139 of SEQ ID NO: 1 and specifically SEQ ID NO: 9.

The instant specification as filed provides only general guidance for the various antisense based nucleic acid compounds used in the claimed method. The specification provides general methodologies for determining effective sequences for the nucleic acid compounds used in the method and provides general methods for delivery of compounds in a treatment, for example (see pages 24-33). Example 8 of the specification shows that the recombinant over expression of AD7c-NTP in cells in culture produces phenotypes associated with Alzheimer's disease neurodegeneration (see page 46, for example). It is noted that it is not clear what particular AD7c-NTP was used in the example since "AD7c-NTP" is defined by the instant specification to include

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variants (see page 17, for example). The specification states at page 18 that because AD7c-NTP is associated with Alzheimer's disease it can be used to screen for drugs to treat neuroectodermal tumors, malignant astrocytomas and glioblastomas. The specification provides no specific guidance for the treatment of the above diseases via antisense based nucleic acid compounds.

The instant specification does not provide any specific guidance such as what particular antisense or ribozyme could be used effectively in the claimed method. The instant specification does not provide guidance or examples that would show by correlation what sequences of antisense based nucleic acid compounds of the method would predictably provide for treatment of disease in general or for the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas specifically. The instant specification does not provide guidance or examples that would show by correlation what modes of delivery would predictably provide for a treatment of disease in general and for the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas in particular. The instant specification does not provide any examples of inhibiting AD7c-NTP in cells in culture or in an animal or provide guidance that would show by correlation the treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas via the administration of antisense based nucleic acid compounds. The specification provides a system that may screen for compounds that may inhibit AD7c-NTP, but the specification has failed to provide one in the art a means to predictably make a nucleic acid based compound used in the claimed method of treatment or prevention such that no undue experimentation would be required in the

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making of the compound (ie selection of a predictable effective [in vivo] sequence) and further how to deliver such a compound in a whole animal such that one would be able to treat neuroectodermal tumors, malignant astrocytomas and glioblastomas without undue trial and error experimentation.

The art of nucleic acid based therapies is an unpredictable art. Agrawal [TIBTECH, Vol. 14:376-387, October 1996] states the following: " [t]here are two crucial parameters in drug design: the first is the identification of an appropriate target in the disease process, and the second is finding an appropriate molecule that has specific recognition and affinity for the target, thereby interfering the disease process" (page376); "[o]ligonucleotide must be taken up by cells in order to be effective. [s]everal reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides {*The instant specification fails to provide any guidance or examples that show an uptake of nucleic acid compound that would correlate to a predictable treatment of neuroectodermal tumors, malignant astrocytomas and glioblastomas, for example*}. Cellular uptake of oligonucleotides is a complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum . . . [i]t is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency." (Page 378); "[m]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations." (Page379); "[a]ny antisense activity observed in such artificial systems [cell culture] should be

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scrutinized carefully with respect to the disease process and its applicability to *in vivo* situations.” (Page 379). The instant specification fails to consider the problems asserted above, for example. The specification fails to provide any particular guidance on how to deliver adequate oligonucleotides to a specified target cell such that there is a treatment of the recited diseases. Furthermore the specification has not even shown any particular cancer disease that has as its causation, an overexpression of AD7c-NTP.

Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: “[a]ntisense molecules and ribozymes capture the imagination with their promise of rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven.”; “[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. [t]his is a challenging quest.”; “[h]owever, their unpredictability confounds research applications of nucleic acid reagents.”; “[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules.”; “Years of investigation can be required to figure out what an ‘antisense’ molecule is actually doing, . . .”; “Because knowledge of their underlying mechanism is typically lacking, non-antisense effects muddy the waters.”; “because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a

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compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known.”; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range.”; “[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells.”; “[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible.”; and, “[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . . [i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*.”

Jen et al [STEM CELLS Vol. 18:307-319, 2000] discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert “[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive.” It is also stated “[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to

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be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

It is clear from the reference above that the art of antisense based therapy is an unpredictable art where the determination of effective sequences and modes of delivery are clearly not routine where one in the art requires specific guidance for any antisense based treatment of any particular disease, for example. One in the art would be required to engage in undue trial and error experimentation to practice the claimed invention since the specification as filed has failed to provide any particular sequences of the various antisense based compounds recited in the claim that would predictably be effective in the treatment or prevention of neuroectodermal tumors, malignant astrocytomas and glioblastomas and also fails to provide with any particularity how one would specifically treat neuroectodermal tumors, malignant astrocytomas and glioblastomas with antisense based nucleic acid compounds. One in the art is left to trial and error experimentation to practice the claimed invention.

(10) Response to Argument

Appellants argue that the scope of the present claims is commensurate in scope with the teachings of the specification and the prior art. It is the examiners position that the scope of what is claimed is outside the scope of what is taught in the specification and the knowledge of one skilled in the art. Appellants argue that the scope of the invention is not broad since the claims are limited to the treatment of an animal in need of treatment of neuroectodermal tumors, malignant astrocytomas, or glioblastomas and also specifies the characteristics of the antisense oligonucleotides and ribozymes. It is noted that even to such a limited target one in the art would be required to de novo/empirically screen thousands of potential antisense oligonucleotides and ribozymes where the specification does not exemplify or identify any specific cancer that is caused or been shown to be treatable as claimed. The specification shows does not identify any particular cancer where the inhibition of an NTP activity or expression is ameliorative. Appellants are left to identify these specific conditions on their own.

Appellant asserts that the art of antisense-based therapy ["antisense based therapy" and "antisense" will be used and includes ribozymes since ribozymes are antisense based therapeutics] was well established at the time of invention. It is noted that the specification cites several methods of providing antisense to cells and to organisms. None of these methods has been shown in the art to be a routine and predictable means of delivery for all antisense application (e.g. for treating any particular disease). Appellant notes that there are successful applications of antisense noted in

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the art. This has not been disputed, but it is not agreed that these successes are demonstrative of a well-established and predictable art. Appellant cites Galderisi et al and Agrawal et al to show success. It is noted that these examples have been treated in the rejection of record. It is noted also that the Agrawal examples are directed to models and do not show the success in the treatment of any disease *per se*. Both of the references discuss the successes in the art and both still indicate that much needs to be developed to make the application of antisense therapy predictable. Appellant also asserts that Galderisi provides a discussion of Vitravene™ as an example that the art is well established. The antisense oligonucleotide of Vitravene™ is administered intravitally and does not suffer from the problems associated with delivery as asserted in the rejection of record.

Appellant asserts that the use of antisense for therapeutic purposes is predictable. Appellant asserts that although various considerations are taken into account in selecting an antisense sequence and deciding upon an appropriate method of cellular delivery, the specification provides substantial guidance regarding these aspects. It is the examiners position the specification provides general options of where one might start without any specific guidance on how to treat a specific disease with a predictable delivery means with an antisense oligonucleotide that would predictably function in its targeted environment. Furthermore the art relied upon in the rejection clearly demonstrates that one in the art would not predict that any particular mode of delivery would routinely function in any of a variety of applications (e.g. various diseases that manifest in various tissue and/or cell types). Appellant argues that target sequence

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selection would have been highly predictable in view of the claim language and the teachings in the specification. It is noted that the rejection of record addresses this argument by showing that even though the type of experimentation required to practice the invention more broadly than exemplified is a factor in the enablement analysis, it is not dispositive. In this case, the more or less standard (albeit empirical and unpredictable) nature of screening for an active antisense in cells and the non-routine experimentation required to find a means of providing a sufficient amount of an antisense that will be effective in an animal and targeted to a specific tissue and/or cell for sufficient time to treat a condition required to expand the scope of an enabled invention is outweighed by the sheer quantity of experimentation to practice the full scope of the claims, the unpredictability of the art generally and the claimed method in particular, and the lack of guidance in the specification regarding the direction in which the experimentation should proceed. The use of the specific oligonucleotides SEQ ID NO: 9, 10, and 11, do not rectify the lack of guidance for delivery, for example.

Appellant also argues that cellular delivery of antisense oligonucleotides was predictable at the time of filing. Delivery to cells in culture was indeed more predictable than delivery to an animal as is made clear from the references and the rejection of record. The claimed invention is drawn to delivery to an animal not cells in culture.

Appellant asserts that the examiner has failed to establish that the art of antisense therapeutics is unpredictable. Appellant argues that the Agrawal reference deals with the unpredictability of antisense in cells in culture, but it is noted that the instant specification fails to provide even cellular data, for example. Applicant asserts

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that the Branch reference teaches that non-antisense effects might be advantageous, however, there has been no disclosure of or discussion of non-antisense in the instantly claimed invention being an advantage that overcomes the unpredictability of the art, for example. Appellant essentially argues, in the treatment of the cited references, that routine experimentation is all that would be needed. Appellant cites the specification at pages 26, 30, 31 and 32 to show that the specification provides guidance for delivery. It is noted that the text is general and requires one in the art to make de novo determinations for a suitable delivery means for any particular disease where there is no specific guidance for the treatment of any particular disease, for example.

In a nut shell, the prior art cited by the examiner and that cited by appellant shows that screening for antisense that function in cells is empirical and that once an antisense is found to be effective in cells in culture it is not then predictable that it will function in an *in vivo* setting and then on top of that the prior art teaches that experimentation needs to be done to find means to effectively deliver antisense in vivo before antisense therapy is routine. The instant specification does not provide sufficient guidance such that one of skill in the art would be able to practice the claimed invention without performing undue experimentation to overcome the above. It is interesting to note that in the same references that applicant cites as providing evidence by pointing to studies in animal models also indicate that much work needs to be done in order for antisense therapeutics to be realized.

Appellant argues that the general disclosure of antisense methodologies of the specification is sufficient to enable the full scope of the claimed invention since the

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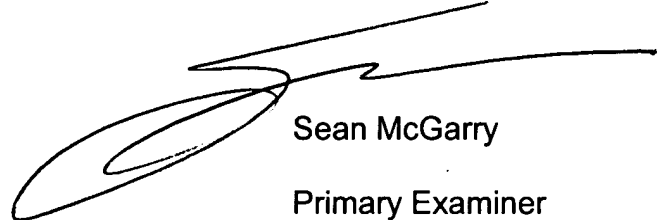
particularities of antisense based therapy would have been available to one in the art at the time of invention. Appellant asserts that it is the burden of the examiner to set forth a reasonable basis to question the enablement provided for the claimed invention. The rejection of record is believed to provide the required reasonable arguments and evidence. Appellant argues that a skilled artisan would appreciate that antisense based compounds function by recognizing complementary or corresponding nucleotide sequences to inhibit translation or transcription. This is part of the process since one would need to deliver a sufficient amount of such antisense based compounds to a particular target cell and further be assured that the antisense will find the targeted region accessible in the environment of required action. A treatment of a particular disease requires more than the establishment that an antisense oligonucleotide may have the capacity to inhibit a target gene but also includes the determination that the capacity is realized in the therapeutic (in vivo) setting and also a mode to provide a sufficient amount to the required cells or tissues. It is not disputed that antisense may be used in treatment of disease, but the amount of guidance required to perform such treatment without undue trial and error experimentation in view of the state of the art is high. Appellant has argues particularities of the cited references, but it is clear when the references are taken as a whole that the state of the art of therapy via antisense is an unpredictable art. Even the reference [Galderisi] cited by applicant concludes "the use of antisense to modify gene expression is variable in both its efficacy and reliability. . . . [m]ost of these concerns can be overcome by the development of a **new generation of**

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antisense molecules with improved target specificity and enhanced delivery to the target cells (emphasis added).

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,



Sean McGarry


Primary Examiner

AU 1635

Conferees:

Andrew Wang

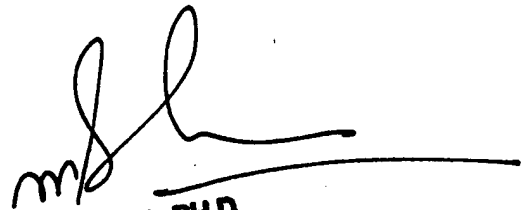
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